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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,184	07/17/2006	David Morton	478.1077	9629

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EXAMINER
OLSON, ERIC

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/571,184	MORTON ET AL.	
	Examiner	Art Unit	
	ERIC S. OLSON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-11,13-28 and 30-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-11,13-28 and 30-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted March 9, 2009 wherein claims 1, 6, and 43 are amended and claims 5, 12, and 29 are cancelled. This application is a national stage application of PCT/GB04/03932, filed September 15, 2004, which claims priority to foreign applications GB0321611.6, filed .September 15, 2003, and GB0327723.3, filed November 28, 2003.

Claims 1-3, 6-11, 13-28, and 30-46 are pending in this application.

Claims 1-3, 6-11, 13-28, and 30-46 as amended are examined on the merits herein.

Applicant's amendment, submitted November 5, 2008, with respect to the rejection of instant claims 1-3 and 9-46 under 35 USC 112, first paragraph, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to limit the mucoactive agent to glycosaminoglycans. Therefore the rejection is withdrawn.

Applicant's amendment, submitted November 5, 2008, with respect to the rejection of instant claims 26 and 29 under 35 USC 112, first paragraph, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to limit the diseases treated to certain specific pulmonary diseases that are enabled by the specification. Therefore the rejection is withdrawn.

Applicant's amendment, submitted November 5, 2008, with respect to the rejection of instant claims 1-3 5-10, 15, and 25-29 under 35 USC 102(b) for being anticipated by Ahmed et al., has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to require the presence of an amino acid in the composition. Therefore the rejection is withdrawn.

Applicant's amendment, submitted November 5, 2008, with respect to the rejection of instant claim 13 under 35 USC 103(a) for being obvious over Ahmed et al. in view of Stossel et al., has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to require the presence of an amino acid in the composition. Therefore the rejection is withdrawn.

Applicant's amendment, submitted November 5, 2008, with respect to the rejection of instant claim 11 under 35 USC 103(a) for being obvious over Ahmed et al. in view of Trofast et al., has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to require the presence of an amino acid in the composition. Therefore the rejection is withdrawn.

The following rejections of record in the previous action are maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-10, 14-30 , 40-42, and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahmed et al. (PCT international publication WO99/06025, reference of record in previous action) in view of Staniforth. (PCT international publication WO97/03649, of record in previous action)

Ahmed et al. discloses a method of treating conditions characterized by late phase allergic reactions (e.g. late phase asthma) by administering an ultra-low molecular weight heparin, or ULMWH. (p. 6 line 14 – p. 7 line 15) Because the composition is able to diminish bronchial hyper-reactivity after antigen challenge to the patient. (p. 7 lines 1-4) one of ordinary skill in the art would see it as being useful for treating an acute asthma attack. The ULMWH has little or no anticoagulant activity and is administered as a pharmaceutical composition which is an inhalable powder. (p. 7 lines 16-21) Besides ULMWH, the inhalable compositions can also comprise other sulfated polysaccharides such as dermatan sulfate, chondroitin sulfate, pentosan polysulfate and/or other glycosaminoglycans and mucopolysaccharides. (p. 20 lines 1-10) Suitable powder compositions include compositions of heparin intermixed with inert powders such as lactose and delivered through an inhaler device. (p. 21 lines 14-19) Other claimed properties of the powder, namely its utility in certain therapeutic indications as recited in claims 25-28, are present in these pharmaceutical compositions, as they are identical to those disclosed in the instant specification to be useful for treating these diseases. Ahmed et al. does not disclose compositions

comprising the specific particle sizes or additives included in the aforementioned claims, or a method comprising spray drying said composition.

Staniforth discloses a powder for use in a dry powder inhaler comprising an active material and an anti-adherent material, where the active material makes up at least 60% of the weight of the powder. (p. 4 lines 6-11) The active material used in these compositions can be a carbohydrate, for example heparin. (p. 11 lines 21-22) Anti-adherent materials can include additives such as leucine, an amino acid, or lecithin, a phospholipid, which are force control agents according to the limits of the instant claims, and additional additives such as lactose. (p. 5 line 32 – p. 6 line 9) N-acetyl-L-cysteine is another additive that can be used. (p. 9 lines 34-37) In a preferred embodiment at least 90% of the composition is made up of particles of active agent (fine particles) which have a diameter of about 0.1-5 μm. (p. 8 lines 26-36) Example 1 discloses a dry powder mixture wherein the active agent particles have a MMAD of 2.1 μm with about 1% leucine by weight. (p. 18 lines 1-21) The optimal size for the agglomerates of active agent and carrier particles is at least 45 μm, indicating that it is preferable to use carrier particles of at least 45 μm. (p. 5 lines 11-27)

It would have been obvious to one of ordinary skill in the art at the time of the invention to make a powder composition of ULMWH of the type described by Ahmed et al. incorporating anti-adherent particles as described by Staniforth, and to use the composition for treating late-phase asthma. One of ordinary skill in the art at the time of the invention would have been motivated to incorporate the anti-adherent particles described by Staniforth because Staniforth discloses that the anti-adherent particles

improve delivery of active agents by inhalation. One of ordinary skill in the art would have reasonably expected success because Staniforth discloses that these methods can be used to formulate inhalable powders for the delivery of heparin.

Furthermore, with respect to the specific particle size of claim 23 or composition of claim 43, one of ordinary skill in the art would have recognized that the disclosure of Staniforth covers a broad range of particle sizes and compositions, and would have been able to adjust the specific amounts with in the disclosed ranges to arrive at the optimal value within the prior art disclosure. Doing so is well within the ordinary and routine level of skill in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted March 9, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the references do not disclose or suggest a composition comprising a glycosaminoglycan and an amino acid as active agents. Specifically, although Applicant admits that Staniforth et al. discloses leucine as an anti-adherent agent, Applicant argues that the claims require that the amino acid be an active agent. However, the term "active agent" does not recite any specific structural feature of the invention, but rather a property that is the result of including an amino acid in the invention. According to MPEP 2144, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by

applicant. >See, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings.");< In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991) The claims therefore include all compositions having a glycosaminoglycan and an amino acid regardless of the specific reason that the amino acid was included. Therefore the rejection is deemed proper and made **FINAL**.

Claims 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahmed et al. (PCT international publication WO99/06025, reference of record in previous action) in view of Staniforth (PCT international publication WO97/03649, of record in previous action) as applied to claims -3, 6-10, 14-30 , 40-42, and 44-46 above, and further in view of Dunbar et al. (Reference included with PTO-892)

The disclosure of Ahmed et al. in view of Staniforth is discussed above. Ahmed et al. in view of Staniforth does not disclose a method wherein the particles of heparin are spray dried at a controlled velocity of less than 20 m/s or one where the droplets are generated by an ultrasonic nebuliser.

Dunbar et al. discloses a method of spray drying that can be used to form dry powder aerosol formulations for inhalation, using either an ultrasonic nebuliser or an airblast nebuliser. (p. 434, left column paragraphs 1-2) The droplet velocities produced by the ultrasonic nebuliser ranged from 0.47-1.09 m/s. (p. 436, right column last paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to make the powders as taught by Ahmed et al. in view of Staniforth by spray drying using an ultrasonic nebuliser. One of ordinary skill in the art would have been motivated to make the particles by this method because Dunbar et al. discloses that spray drying using an ultrasonic nebuliser is a suitable method for making inhalable dry powders having the required properties. One of ordinary skill in the art would reasonably have expected success because spray drying is a common and well-characterized method of making pharmaceutical powder formulations.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted March 9, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are the same as those made with respect to Ahmed et al. in view of Staniforth above, and are not found to be persuasive for the same reasons. Therefore the rejection is deemed proper and made **FINAL**.

Claims 11 and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahmed et al. (PCT international publication WO99/06025, reference of record in previous action) in view of Staniforth (PCT international publication WO97/03649, of record in previous action) as applied to claims -3, 6-10, 14-30 , 40-42, and 44-46 above, and further in view of Chickering et al. (US pre-grant publication 2004/0121003, cited in PTO-892)

The disclosure of Ahmed et al. in view of Staniforth is discussed above. Ahmed et al. in view of Staniforth does not disclose a method wherein the particles of heparin are jet milled at an inlet pressure of 0.1-3 bar or 2-12 bar, or wherein at least 90% by volume of the active particles are less than 20 μm in diameter prior to jet milling.

Chickering et al. discloses a method for making a dry powder blend comprising jet milling particles of a pharmaceutical active agent with larger particles of an excipient. (p. 1 paragraph 0009) Excipient particles are preferably 40-100 μm in diameter and can include sugars and amino acids, such as lactose, mannitol, leucine, or cysteine. (pp. 1-2, paragraph 0010) The microparticles to be jet milled can be formed by spray drying. (p. 2 paragraph 0013) The process substantially maintains the size and morphology of the individual microparticles while deagglomerating them. The jet mill can be operated at any pressure between 0 and 10 bar. (p. 10 paragraph 0130)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the jet milling procedure of Chickering et al. to prepare a particle blend as described by Ahmed et al. in view of Staniforth. One of ordinary skill in the art would have been motivated to use this method because Chickering et al. already discloses

that the method is useful for making a blend of fine active particles with carrier particles. One of ordinary skill in the art would have reasonably expected success because jet milling is already known in the art as a routine method of making pharmaceutical powders.

With regard to the initial particle size listed in instant claim 39, one of ordinary skill in the art would have recognized that since the jet milling process substantially preserves the size of individual particles, the active particles used in this process should already be of the desired size, which is much less than 20 μm.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted March 9, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are the same as those made with respect to Ahmed et al. in view of Staniforth above, and are not found to be persuasive for the same reasons. Therefore the rejection is deemed proper and made **FINAL**.

Applicant's amendment necessitates the following new grounds of rejection:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ahmed et al. (PCT international publication WO99/06025, reference of record in previous action) in view of Staniforth (PCT international publication WO97/03649, of record in previous action) as applied to claims -3, 6-10, 14-30 , 40-42, and 44-46 above, and further in view of Stossel et al. (US patent 5464817, cited in PTO-892)

The disclosure of Ahmed et al. in view of Staniforth is discussed above. Ahmed et al. in view of Staniforth does not disclose a composition comprising rhDNAse.

Stossel et al. discloses a method of disaggregating actin, reducing the polymerization of free actin, and inhibiting the binding of actin to DNAse I, said method comprising administering an actin binding compound to the respiratory tract of a subject. (column 5 lines 45-65) This method can include addition of exogenous DNAse (column 6 lines 47-51) or preferably gelsolin or thymosin β4. (column 12 lines 29-34) Diseases treatable in this manner include various pulmonary diseases such as cystic fibrosis, chronic bronchitis, mucopurulent or purulent exacerbation of simple mucoid bronchitis, bronchorrhea, bronchopneumonia, widespread bronchiolitis, purulent pneumonia, pneumonic-alveolar-consolidation, asthma, with or without asthmatic bronchitis with mucus plugging, acute and/or chronic purulent sinusitis, empyema, bronchiectasis, bronchocoele, adult respiratory distress syndrome (ARDS), post-transplantation obliterative bronchiolitis, and allergenic bronchiolitis (fibrosing alveolitus), for example.

(column 7 lines 11-21) These drugs can be administered by inhalation. (column 10 lines 62-67)

It would have been obvious to one of ordinary skill in the art at the time of the invention to add gelsolin or thymosin β4 to the therapeutic compositions of Ahmed et al. in view of Staniforth One of ordinary skill in the art would have been motivated to make the combination because Stossel et al. discloses these compounds to be useful for treating the same indications as the compounds of Ahmed et al., namely pulmonary diseases such as asthma. One of ordinary skill in the art would reasonably have expected success because combining two known prior art compositions known to be useful for the same purpose is well within the ordinary and routine level of skill in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted March 9, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are the same as those made with respect to Ahmed et al. in view of Staniforth above, and are not found to be persuasive for the same reasons. Therefore the rejection is deemed proper and made **FINAL**.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ahmed et al. (PCT international publication WO99/06025, reference of record in previous action) in view of Staniforth (PCT international publication WO97/03649, of record in

previous action) as applied to claims -3, 6-10, 14-30 , 40-42, and 44-46 above, and further in view of Trofast. (US patent 6027714, of record in previous action)

The disclosure of Ahmed et al. in view of Staniforth is discussed above. Ahmed et al. in view of Staniforth does not disclose a composition comprising mannitol or glucose.

Trofast discloses a composition for inhalation comprising budesonide and a carrier substance. (column 1 lines 23-28) The carrier substance is preferably a saccharide such as glucose or a sugar alcohol such as mannitol. (column 1 lines 34-39)

It would have been obvious to one of ordinary skill in the art to use glucose or mannitol as an inert powder carrier in the compositions of Ahmed et al. in view of Staniforth One of ordinary skill in the art would have been motivated to use these specific carriers because Trofast already discloses that they are useful as inert carriers for inhalable dry powders. One of ordinary skill in the art would reasonably have reasonably expected success because Ahmed et al. already disclose that any conventional inert carrier substance can be used in the disclosed compositions.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted March 9, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are the same as those made with respect to Ahmed et al. in view of Staniforth above, and are not found to be

persuasive for the same reasons. Therefore the rejection is deemed proper and made **FINAL**.

Conclusion

No claims are allowed in this application. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. OLSON whose telephone number is (571)272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
5/15/2009

/Shaojia Anna Jiang/
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